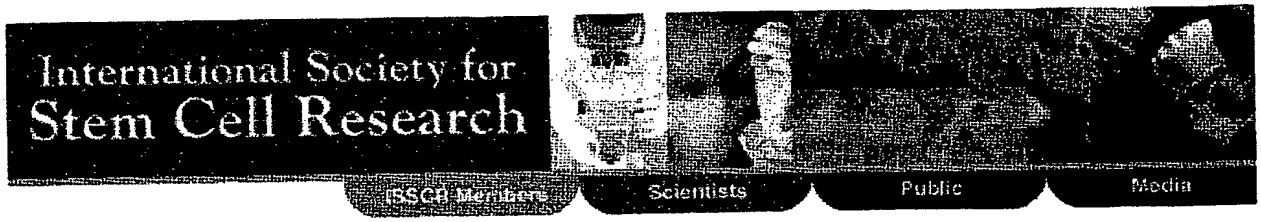

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Stem Cell Therapy Symposium Heinrich Heine University

By Christian van den Bos and Doug Sipp (ISSCR International Committee)

The conference was organized into several sessions focusing among others on somatic stem cells, tissue engineering, regeneration of bone and connective tissue, and stem ce and cell-based therapies for hepatic, neurological and cardiac diseases (experimental and clinical). A summary of selected talks follows.

SOMATIC STEM CELLS

ER Burchardt described the application of CD133+ cells to cardiac regeneration. A rat model of left anterior descending (LAD) coronary artery occlusion to which CD133+ cell were applied revealed the participation of those cells in vessel formation. Burchardt further described the development of a procedure in which the patients' CD133+ cells were harvested and grafted in a single session, the procedure taking as little as 2.5 hours. 80 patients have been treated thus far. Klein et al., *Cytotherapy*, in press.

A Stold described the use of CD133+ cells for therapies aimed at restoring platelet function. He delineated expression patterns of platelets derived from megakaryocytes and the derivation of platelets from transfected stem cells in which the resulting platelets carried the marker genes.

TISSUE ENGINEERING AND ARTIFICIAL ORGANS

A Baader presented bioreactor systems for generating large quantities of stem cells and other cell populations such as chondrocytes; the latter are also biomechanically stimulated. Additional applications included the generation of cells for canine heart valves, porcine liver cells as well as an extra-corporeal liver system.

RG Bretzel presented on the use of cell treatment for diabetes mellitus, specifically, the replacement of islet cells. He discussed ongoing mature islet transplantation efforts, with more than 620 cases worldwide and 82 thus far in Giessen, Germany. The Edmonton protocol has yielded insulin independence in 5 of 13 patients. The onset of diabetes was discussed in the context of autoimmune reactions as reported by Rossini (*Diabetes*, 2004).

G Rau discussed the use of scaffolds in generating implants. The basic technologies involve the use of scaffolds, such as those based on the Matricell technology, sandwich structures and encapsulated spheres. Applications included generating bladder walls, plastic surgery and guided nerve regeneration with or without macroporous structures.

REGENERATION OF BONE AND CONNECTIVE TISSUE

AK Boßerhoff described the differentiation of mesenchymal stem cells (MSCs) into chondrocytes and the accompanying changes in gene expression patterns. In particular she described the expression and properties of the molecule MIA, a secreted 11 kDa protein found specifically in chondrogenic differentiation. Histological analysis of mouse embryos demonstrated its expression in spine and ribs as well as other tissues. MIA wa present in chondrocytes, but absent in osteoblasts.

STEM CELL THERAPY FOR HEPATIC REGENERATION

W Knoepfel presented on the use of CD133+ cells for liver regeneration and provided a

overview of the cells' properties and approaches to formulating therapies based on their biologic properties. Liver regeneration using stem cells may be useful since residual live weight post resection needs to be at least 0.6% of total body weight in order to maintain physiological function. In cases of malignant growths, sometimes there is not enough time to perform multi-step resections and so other ways of increasing the amount of live tissue are desirable. In particular, CD133+ cells were applied through the portal vein an large parts of the right lobe were removed once the size of the left lobe was increased.

H Fiegel described the ex-vivo expansion of liver cells. In particular, he described the experimental use of mesenchymal stem cells (MSCs) that were GFP-transduced and co cultured with hepatocytes. These co-cultured MSCs were then identified by flow cytometry exploiting their green fluorescence and analyzed for Thy-1 and liver marker expression demonstrating partial positivity for liver markers.

G Fürst described means to follow stem cell grafts using advanced radiological imaging techniques in combination with clinical stem cell therapy. Tools applied included CAT scans and NMR using iron oxide particles.

STEM CELL THERAPY FOR NEUROLOGICAL DISEASES

HW Müller described the potential of umbilical cord blood stem cells termed unrestricted somatic stem cells (USSCs) for neural regeneration. USSCs were differentiated in vitro towards neural lineages and were able to give rise to dopaminergic cells as demonstrated by histochemical evidence for the presence of the required enzymes. For in vivo assessment of the neural potential of USSCs the latter were injected stereotactically into rat brains following labelling with a fluorescent dye. Several weeks later histological analyses revealed the presence of labelled cells at sites distinct from the injection site suggesting active migration of injected USSCs. Further, cells staining selectively for human tau protein were detected suggesting neural differentiation of injected USSCs.

A Saleh described brain imaging approaches on the cellular level. Macrophages were loaded with iron oxide particles and observed in rat cortical lesions. Macrophages appeared to transport the contrast agent across the blood-brain barrier.

CELL BASED THERAPY FOR CARDIAC DISEASES: EXPERIMENTAL RESULTS

T Brand described the roles of WNT and BMP molecules in embryonal cardiac development . In particular, the POPDC (Popeye domain containing gene) proteins, such as POPDC1, which accumulates at the cell-cell interface, were discussed.

RK Li described cellular transplantations into infarcted heart tissue and reviewed that a broad selection of cells had been tested successfully. These cells may affect heart function by secreting molecules of the extracellular matrix. One example of this may be the TIMPs, which hinder metalloproteases and hence slow down remodelling processes

A Ruhparwar presented on epicardial gene therapy and laser revascularization therapy. He raised the possibility of biological pacemakers circumventing the problems associate with conventional ones. He described work in which fluorescently labelled fetal cardiomyocytes had been implanted into dogs carrying x-linked muscular dystrophy. Thi model was then used to test several cell types, including skeletal myoblasts, fetal cardiomyocytes, ES cells and bone marrow derived pluripotent cells.

CELL BASED THERAPY FOR CARDIAC DISEASE: CLINICAL RESULTS

GP Meyer gave a talk on the BOOST trial of stem cell therapy following myocardial infarction. Patients received autologous bone marrow cells intracoronarily in a randomized fashion 5-6 days post infarction (Lancet, 2004). Following this procedure, n signs of additional ischemic events were observed nor were any other adverse advents, so that the approach is deemed safe. Tests of efficacy showed that the ejection fraction was elevated by 6-7%.

V Schächinger described stem cell therapy for cardiac regeneration using either circulating endothelial progenitor cells or bone marrow cells. A 1-year follow up indicate that 97% of the patients remained event-free and that both groups had improved by 8-1 % over patients not treated in this fashion. The coronary flow reserve in infracted vessel

returned to normal 4 months post treatment.

C Pompilo described a clinical trial using mobilized CD133+ cells for the regeneration of ischemic myocardium. Patients were followed for 6 months after having received 13-200x10^6 cells. Endpoint measurements included wall movement and perfusion, both o which were found to be improved. The comparative benefits to the patient of apheresis and bone marrow aspiration were discussed.

G Kadipasaoglou spoke on the "Texas heart experience", i.e., activities at the Houston medical center. A cell therapy study involving the intracoronary application of bone marrow cells in a canine model was presented (to be published by Geng et al). 30 days post application stem cells were detected and contributed to the formation of new vessels. Transendocardial application was discussed and a study testing this route of application was presented. Cell types other than those derived from bone marrow were also discussed, including endothelial cells, smooth muscle cells and chondrocytes (for seeding on artificial surfaces and cells genetically altered to, for example, express VEGF).

A Ghodsizad spoke on the combination of bone marrow cell therapy with transmyocardi laser revascularization. A procedure to obtain autologous CD133+ cells that utilized 60-330 ml of bone marrow from the iliac crest and yielded 150-205 x10^6 CD133+ cells wa presented (Klein & Ghodsizad, *Cytotherapy*, in press). Functional improvements were observed and it was suggested that new vascularization had taken place within the channels created by laser treatment. The choice of patients (left ventricular ejection fraction (LVEF) of about 30%) was commented on positively by members of the audience, who suggested it might provide a particularly stable baseline.

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